



A comparison of HFA-BDP AutohalerTM with budesonide Turbuhaler[®] in asthma control of adult patients with mild to moderately severe disease

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Introduction

Hydrofluoroalkane-134a (HFA) beclomethasone dipropionate (BDP) extrafine aerosol is a pressurized metered dose inhaler (pMDI) available for the treatment of asthma. Unlike most pMDIs, HFA-BDP is a solution, rather than a suspension, of BDP in HFA propellant. This reformulation, combined with improvements in inhaler technology, results in the production of aerosol particles of smaller mean mass aerodynamic diameter (MMAD) than produced from chlorofluorocarbon (CFC)-BDP inhalers, 1.1 μm vs. 3.5–4 μm , respectively (1,2).

Inhaled corticosteroids are increasingly recommended for first-line therapy in the management of asthma (3,4) with pMDIs the most commonly prescribed method of delivery. However, a significant proportion of patients fail to use pMDIs correctly, even with appropriate training. It has been reported that 50% of patients revert to their previous incorrect press and breathe inhaler technique following proper training (5).

HFA-BDP as the AutohalerTM (AH) inhalation device has been shown to be of clinical benefit to patients with problems handling a press and breathe pMDI (6). Dry-powder inhalers (DPIs) such as the budesonide Turbuhaler[®] (BUD TH), have also been designed to limit the handling difficulties encountered with traditional pMDIs. However, in contrast to HFA-BDP AH, DPIs remain breath dependent (i.e. drug delivery from the inhaler is dependent on inspiratory flow) (Fig. 1) (7).

While comparative dosing strategies for HFA-BDP AH and BUD TH have not yet been investigated, it is recognized that CFC-BDP and budesonide have similar therapeutic efficacy and safety profiles. In the past, these agents have been considered to be equipotent (9,10), but recently budesonide has been recognized to be somewhat more potent, especially if administered via the Turbuhaler[®] (3,11). Given this, and the fact that HFA-BDP produces equivalent efficacy to CFC-BDP at approximately 2.5-times the daily steroid dose (12) it can be hypothesized that half the daily dose of HFA-BDP AH would provide equivalent control of asthma symptoms to the BUD TH. The

following two studies (13,14), performed in patients with different severity of asthma were designed to test this hypothesis. Prior to the studies, all patients showed a defined degree of symptoms of asthma despite receiving a small (study 1 including patients with mild to moderate asthma) or mid-dose (study 2 including patients with moderate to severe asthma) of inhaled steroids. The doses chosen to improve symptom control were in line with recommendations from the global initiative for asthma (GINA) and normal clinical practice.

HFA-BDP AH vs. BUD TH in patients with mild to moderate asthma

In a 6-week, open label, parallel group, multicentre study 193 patients with mild to moderate asthma (age range, 18–75 years) demonstrated symptomatic asthma on their current therapy (BUD 400 $\mu\text{g day}^{-1}$) during 7 days prior to randomization to HFA-BDP AH 400 $\mu\text{g day}^{-1}$ ($n = 98$; baseline AM PEF 72.3% pred) or BUD TH 800 $\mu\text{g day}^{-1}$ ($n = 95$; baseline AM PEF 73.3% pred).

Between group comparisons revealed equivalent mean changes from baseline for AM PEF (Fig. 2). There were no significant differences in asthma symptom control with respect to the evaluations of a daily asthma symptom score and a sleep disturbance score (Fig. 3). Daily β -agonist use was not significantly different between both groups, however HFA-BDP (400 $\mu\text{g day}^{-1}$) over 6 weeks produced a statistically significant reduction in total daily β -agonist use ($P < 0.05$) (Fig. 4). There were no significant differences in the number/type of adverse events reported. On the basis of these results, Laitinen *et al.* (13) concluded that, in patients with mild to moderate asthma, half the daily dose of HFA-BDP AH (400 $\mu\text{g day}^{-1}$) provided equivalent asthma control to BUD TH (800 $\mu\text{g day}^{-1}$).

HFA-BDP vs BUD in patients with moderate to severe asthma

This was an 8-week, open study in patients with moderate-to-severe asthma (age range, 18–75 years), previously on 500–1000 $\mu\text{g day}^{-1}$ CFC-BDP, or equivalent. After 5–14 days run in, patients were randomized to HFA-BDP AH 800 $\mu\text{g day}^{-1}$ or BUD TH 1600 $\mu\text{g day}^{-1}$. The intent-

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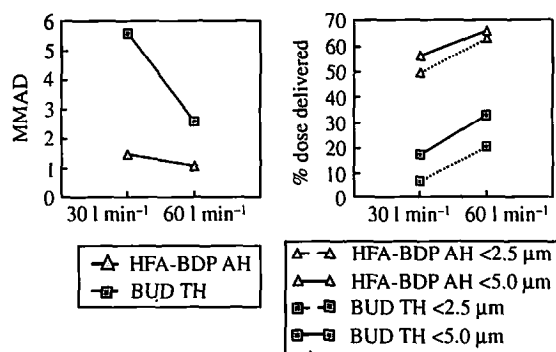


FIG. 1. Flow dependence of particle size for HFA-BDP AH and BUD TH at two different flow rates according to Ross (7). MMAD: mass median aerodynamic diameter.

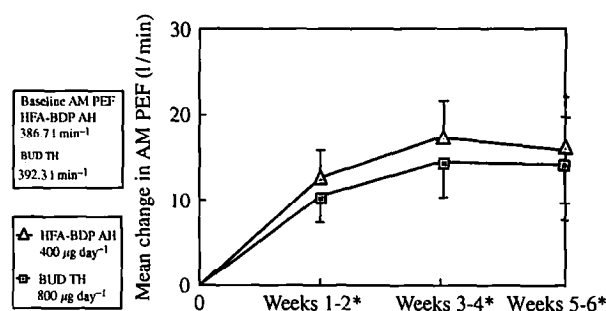


FIG. 2. Mean change from baseline in AM PEF (l min⁻¹) during treatment with HFA-BDP AH (400 μg day⁻¹) and BUD TH (800 μg d⁻¹) according to (13). †: Significant within treatment group change from baseline ($P < 0.01$); *: $P \leq 0.001$ from equivalence.

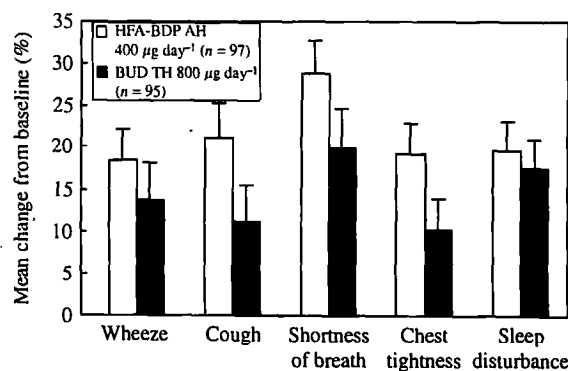


FIG. 3. Mean change from baseline at weeks 5-6 in % of days/nights free from asthma symptoms (13).

to-treat population consisted of 111 patients on HFA-BDP AH (mean age, 49.2 years; AM PEF, 66.7% pred) and 98 patients on BUD TH (mean age, 47.8 years; AM PEF, 67.2% pred).

Mean change from baseline in AM PEF, at week 8 was 23.95 l min⁻¹ for HFA-BDP AH and 24.46 l min for BUD TH (Fig. 5). Furthermore, there were no significant differences in mean change from baseline in FEV₁ or

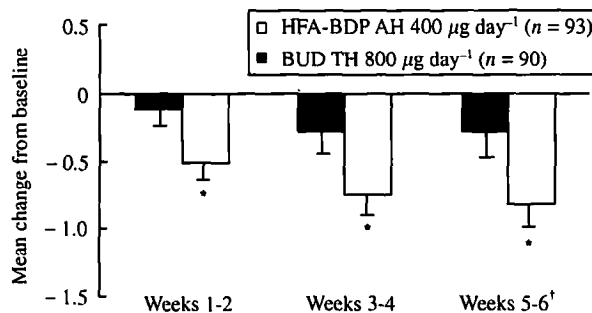


FIG. 4. Mean change in baseline in total β-agonist puffs. *: Within treatment group change from baseline ($P < 0.05$); †: $P = 0.054$, HFA-BDP AH vs. BUD TH.

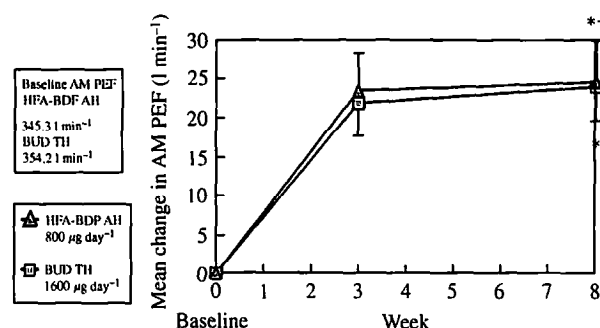


FIG. 5. Mean change from baseline in AM PEF (l min⁻¹) in patients with moderate to severe asthma during treatment with HFA-BDP (800 μg day⁻¹) and BUD TH (1600 μg day⁻¹). †: Significant within treatment group change from baseline ($P < 0.01$); *: $P \leq 0.001$ equivalence.

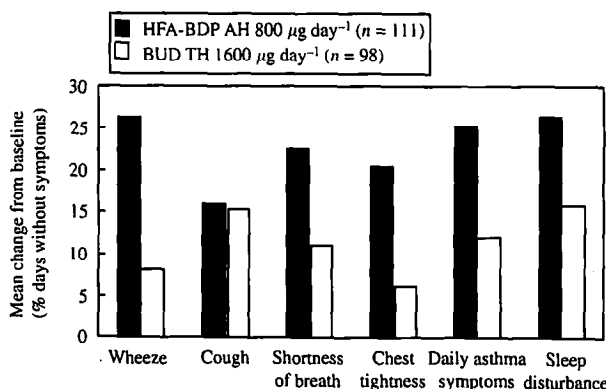


FIG. 6. Mean change from baseline in percentage of days/nights free from asthma symptoms/sleep disturbance at week 8, according to (14). $P < 0.01$ within treatment group change from baseline (mean of the last five days of run-in period). Week 8: mean of the last 5 days after clinical visit in week 8.

β-agonist use. Patients on HFA-BDP AH had a significantly greater mean change from baseline in percentage of days free from shortness of breath ($P = 0.02$), chest tightness ($P < 0.01$) and daily asthma symptoms ($P = 0.03$) at week 8 (Fig. 6).

TABLE 1. Incidence of adverse events possibly or probably related to study medication

Adverse event	HFA-BDP AH 800 µg (n = 111) %	BUD TH 1600 µg (n = 98) %
Dysphonia	5.4	4.1
Fungal infection (oropharyngeal)	2.7	4.1
Increased asthma symptoms	0	2.0
Bronchitis	0	1.0
Inhalation site sensation	0	1.0
Stomatitis	0	1.0
Gingivitis	0.9	0
Weight gain	0.9	0
Cough	0	0
Inhalation taste sensation	0	0

The incidence, type and severity of adverse events were similar in each group (Table 1). At week 8, the mean change from baseline in corrected urine cortisol/creatinine (UCC) ratio in a subgroup of patients was -0.36 for HFA-BDP and -4.88 for BUD TH ($P < 0.01$). In terms of systemic safety, the comparison of UCC ratios, which is as sensitive a measure as overnight urinary cortisol levels, suggested that there had been no clinically relevant decreases in cortisol levels in patients taking either medication during the study. The statistically significant difference of UCC-changes was in favour of HFA-BDP.

Discussion

To improve drug delivery and therapeutic effectiveness in patients with asthma who have difficulty handling a pMDI, breath-actuated inhalers, such as the HFA-BDP AH, and breath-dependent DPIs, such as BUD TH, have been designed.

Both studies looked at whether half the daily dose of HFA-BDP AH produced equivalent control of asthma compared with BUD TH. While the pharmacokinetics and biochemical properties of BUD and BDP are diverse, both agents are commonly used inhaled steroids in the treatment of asthma (15). Both treatments produced within treatment group improvement from baseline AM PEF during the course of the studies, being statistically equivalent for HFA-BDP AH (400 as well as $800 \mu\text{g day}^{-1}$) and BUD TH (800 as well as $1600 \mu\text{g day}^{-1}$).

Symptom assessments are expected to be beneficial in giving an indication of the anti-inflammatory effects throughout all the airways of the lung (16). During the

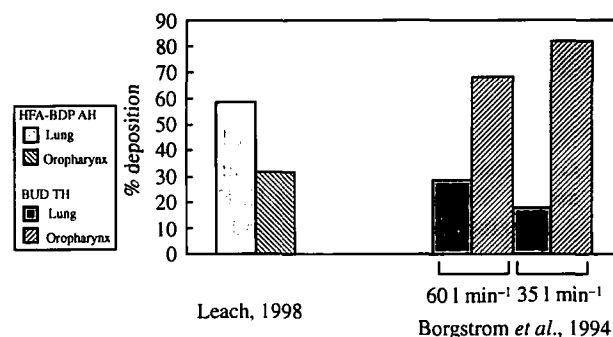


FIG. 7. Deposition of particles of HFA-BDP AH and BUD TH within the lung and the oropharynx (8,17).

study by Worth *et al.* (14) in patients with a greater severity of the disease than in the study of Laitinen *et al.* (13), asthma symptoms improved to a significantly greater extent in patients on HFA-BDP AH compared with patients on BUD TH. A possible explanation for these efficacy results could be differences in the lung deposition pattern of HFA-BDP AH and BUD TH. Improved lung deposition for BUD TH compared with pMDI has been shown, especially when a high inspiratory flow was mandatory (8) (Fig. 6). For BDP, reformulation of BDP in HFA propellant has enhanced drug delivery to the lung periphery, independent of inspiratory flow (17). This phenomenon arises through a combination of factors attributable to the newly designed inhaler technology: particles from HFA-BDP have a smaller mass median aerodynamic diameter (MMAD) than those produced from CFC-BDP pMDI or BUD TH, and the spray is more gentle than in other pMDIs (7,18). Therefore, according to inhaled particle dynamics, less drug should impact on the throat during inhalation and more drug should be capable of penetration to the small airways (Fig. 7).

With regards to tolerability, HFA-BDP AH and BUD TH had similar profiles of side effects profiles in both studies. In all patients under study, drug-related events were predominantly mild-to-moderate in nature and low in frequency. A statistically significant difference was observed, in favour of HFA-BDP AH, between mean change from baseline in corrected UCC at week 8 in a subgroup of the study of Worth *et al.* (14). The clinical advantage of this finding remains uncertain.

In conclusion, HFA-BDP AH at half the daily dose of BUD TH produced equivalent improvement in control of asthma with additional benefits on reduction of asthma symptoms.

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